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Vaccination

Preventive human papillomavirus vaccination

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Considerable gains at the individual and societal level would be obtained if cervical cancer could be prevented

The cancer burden causally associated with human papillomavirus (HPV) infections is high. Cervical cancer is the second most common cancer among females in the world, with 500 000 new cases and 300 000 premature deaths a year.[1] Because of the long preclinical period cervical cancer can be prevented by screening, diagnosis, and treatment of premalignant cervical lesions, but for developing countries preventive vaccination may be the only possibility to significantly reduce cervical cancer incidence. Also in the developed countries considerable gains at the individual and societal level would be obtained, if a significant proportion of cervical cancer and its precursor lesions could be prevented by HPV vaccination (for a systematic review see Lehtinen *et al*[2]). In addition, other anogenital cancers, oropharyngeal and base of tongue cancers, and probably a small proportion of oesophageal cancers are all strongly associated with past HPV infection.[3–5] For these and other possible HPV associated cancers, vaccination may be the only possibility for prevention. Overall prevention of HPV infections may result in a 5–10% reduction of cancer mortality worldwide. This editorial seeks to answer the following two questions: what kind of vaccines will be tested and how should their efficacy be defined?

Preventive HPV vaccines entering clinical efficacy (phase III) trials are plain virus-like particles (VLPs), DNA free capsids comprising the major viral capsid (L1) protein (manufactured by Merck, GlaxoSmithKline, and by NIH), or chimeric VLPs (CVLP), containing various combinations of early viral proteins attached in different ways to the major L1 or the minor (L2) capsid proteins of the virus.

In phase I and II trials HPV VLPs have proved to be safe and highly immunogenic.[6] HPV VLP immunisation induces approximately 100-fold higher neutralising antibody titres than natural infection. The level of mucosal immunoglobulin G (IgG) is 10% but it varies following the menstrual cycle and is lowest at the time of ovulation. The prevailing theory of the mode of action of the vaccine, however, suggests that this variation may not be a major problem. In natural infection the entry of HPV into the basal cells of the epithelium, which support the initial stages of viral replication, is facilitated by a microscopic trauma resulting from, for example, sexual intercourse. Following this micro trauma, circulating antibodies leak to the epithelial surface and neutralise the virus.

The L1 antibodies recognise a conformational, type specific epitope, and have shown close to a 100% protection in animal studies against homologous challenges with both HPV and animal papillomaviruses.[7] While the increasingly large number of oncogenic HPV types (16, 18, 31, 33, 35, 45, 51, 52, 58, 59) that associate with cervical cancer may make it impossible to achieve 100% protection against cervical cancer, it is relatively easy to include the most prevalent oncogenic HPVs (HPV16 and HPV18) into a multivalent VLP vaccine, and even tailor the vaccine composition by the HPV types most prevalent in different geographic areas should this prove necessary.

Analogously to hepatitis B virus (HBV) vaccine HPV VLPs also induce cytotoxic T cell (CTL) responses by entering the MHC class I pathway.[7] If the antibodies fail to neutralise all HPV virions, CTLs recognising viral capsids bound for as long as 10–12 hours to more or less specific cellular receptors (integrin and/or heparan sulphate proteoglycans[8 9]) might block spread of the virus at its most primordial state in the initially infected cells. Production of new virions takes place in the upper layers of the epithelium, and CTLs targeting these cells might effectively reduce spread of the virus. Indication of this has, however, been shown only for the non-oncogenic HPV VLPs, and it is not clear whether such a response is able to eliminate oncogenic HPVs from the basal cells.[10]

CVLPs may offer a significant advantage in this regard. The expression of various early HPV proteins responsible for viral replication (E1), transcription (E2), and oncogenesis (E6, E7) is abundant both in the basal and the differentiating epithelial cells providing good targets for the CTLs. Two vaccines based on different gene constructs—HPV16 L1, L2 truncated E2–E7 CVLP (by an NIH group) and HPV16 L1–E7 CVLP (by Medigene)—have passed or are passing safety and immunogenicity tests. In addition to the induction of high titres of neutralising antibodies, some of which (anti-L2 antibodies) may be cross protective against several HPV types, the CVLP vaccines induce CTL responses against the early proteins in humans.[11] However, for CVLPs data on humans are scarce and need to be expanded. CTL responses against the early HPV proteins are important not only in order to provide theoretically improved protection and possible therapeutic effect, but because they may also offer cross protection against several HPV types. The E1 and E2 proteins are particularly well conserved among the HPVs.

The analogy between the different HPV VLP vaccines and the first human cancer vaccine, HBV vaccine, is very encouraging. The HBV vaccine has an overall efficacy of 95%,[12] and even when given to infants born to mothers with active hepatitis (HBV-e antigen positive women, the offspring of whom are prone to become chronic HBV carriers) its efficacy exceeds 75%. These figures also fit the first available data on long term effects of universal HBV vaccination. The incidence of liver cancer has reduced by 75% among 12–14 year old Taiwanese children 15 years after implementation of the nationwide HBV vaccination programme.[13] This was to be expected on the basis of seroepidemiological data showing that HBs antibody positive

individuals have a reduced risk of liver cancer, whereas HBs antigen positive individuals have an increased risk. This was the first randomised trial proving the efficacy of HBV vaccination against both acute hepatitis B and becoming a chronic HBV carrier. But, however encouraging, analogies should be considered with caution.

While it appears that most of the women treated for the HPV induced premalignant lesions by, for example, laser or loop excision can tackle the residual low amount of virus and eventually clear the infection, recurrences do occur with varying incubation times and for reasons that are not totally understood.[14] Restricting the viral load plays a part, and new strategies for cervical cancer control are also based on identification of women with moderate to high levels but not low levels of oncogenic HPV DNA (for a systematic review see Cuzick *et al*[15]). The role of natural infection or vaccine induced VLP antibodies in restricting mucosal HPV infection may, however, be qualitatively different from the central role of circulating HBV antibodies in preventing systemic hepatitis B infection. While HBV antibody positive individuals have a reduced risk of liver cancer, the HPV16 VLP antibody positive individuals remain at an increased risk of developing cervical cancer and other HPV16 associated cancers 10–20 years after infection.[2–5] There are no good data to suggest that the antibodies would do any harm—for example, by inducing latency, but we simply do not know to what extent the paradigm on prevention of liver cancer by preventing acute HBV infection and HBV carrier status can be applied in the HPV infection-cervical neoplasia context.

The main effector function of VLP vaccination is neutralising antibodies[7] but these may never be able to induce totally sterilising immunity and the concept of significantly reducing the viral load becomes an issue.[16] While the minimum HPV viral load for development of cervical and other cancers is not known, it is highly likely that HPV vaccine induced neutralising antibodies and/or CTLs will prevent or significantly restrict and aid in clearing of the primary HPV infection, and reduce transmission of the infection to others. Randomised clinical trials will eventually define efficacy of the different vaccines against persistent HPV infection and other surrogate end points, such as cervical intraepithelial neoplasia grade II/III. A proof of the principle that HPV vaccines can prevent these necessary steps in cervical carcinogenesis might be considered sufficient to demonstrate efficacy and to compare different vaccines, and limited licensures will be considered probably sooner rather than later.

There are, however, several possible pitfalls that could prevent effective vaccines from actually achieving their expected health benefits. For example, if vaccination failure is preferentially associated with determinants of progression or if vaccination induces changes in the population biology of the different HPV types. To find out these pieces of information one has to organise a long term follow up of the initial randomised trials. Countries with stable and vaccination prone populations, population based health registers, standardised public health care, and organised mass screening for cervical cancer have the appropriate infrastructure and setting for direct extension of the clinical trials to the invasive cervical cancer (ICC) and cervical intraepithelial neoplasia grade III (CINIII) end points based on registry follow up.[17] Population based randomisation and informed consent based linkages of the different study and health registers from the very beginning to death are most important especially to avoid different selection biases, performance bias resulting from "contamination" of the population after licensure of the vaccines,[18] and loss to follow up bias. The ultimate proof will be that immunisation with HPV vaccines significantly reduces the incidence of (and mortality from) cervical cancer and its immediate precursors compared to unvaccinated population based referents.[17] If it turns out that the plain VLP vaccines fail to do it, while the chimeric VLP vaccines are successful we can infer that simple reduction of the HPV load at the port of viral entry is not enough, and that the second barrier of cell mediated immunity against the early viral proteins is also needed. At the moment, however, there is no indication of this and both alternatives should be pursued.

For all end points it would be optimal to target large numbers of young boys and girls who are about to start their sexual activity, since they will have the highest event rates of both HPV infections and associated cancers. Targeting both sexes may, however, not be necessary at this stage since the assumed vaccine efficacy against HPV infection (90%) is high enough to bring the beneficial long term effect to the females.[19] With an assumed attack rate of 0.65% and 60% vaccine efficacy against CINIII+ICC, enrolment of altogether 15 000 such vaccinees and referents for 15–20 years of registry based follow up would give 80% statistical power to judge whether a vaccine which covers two thirds of the oncogenic HPV types protects against CINIII+ICC. Comparison of different HPV vaccines and gradual implementation of the adolescent vaccination into the general vaccination programme using the same setting would bring in considerable synergy and needs to be considered seriously. Last but not least, possible ethical problems associated with ending or discontinuing the early end point clinical trials would be largely solved by the possibility of referring the vaccinees to an organised mass screening.

Pieces of the preventive HPV vaccination puzzle are on the table. If the scientific community, together with the public health authorities and vaccine manufacturers, manages to solve the puzzle the expected health benefits are immense.

Key messages

- DNA free virus-like particle vaccines containing either structural (L1) HPV proteins or both structural and early viral proteins have passed/are passing safety/immunogenicity trials.
- Phase III efficacy trials with the different VLP vaccines using intermediate end points such as protection against HPV positive squamous intraepithelial lesions will start soon.
- Long term follow up of the phase III trials would be important to obtain proof for the vaccine efficacy against cervical cancer.
- Phase III and the long term follow up trials may help future public health policy decision making.

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Editorial

The year ahead

Mohsen Shahmanesh

We have introduced some new sections with the aim of adding value to the journal. *Update* has replaced the *Recent Publications* section and hopes to bring expert critical summary of topic based important recent publications—pelvic inflammatory disease on this occasion. An impending tropical disease section, edited by David Lewis, will provide state of the art summaries of diagnosis and management of these conditions, embracing also issues faced in resource poor settings.

Later this year we will begin our interactive CME section, based on "grey cases." Sarah Edwards will be heading this section helped by Richard Lau. We are negotiating with the Royal College of Physicians to gain CPD recognition. Our expanded editorial board have all promised to provide us with either an *Update* or a review article, and we are waiting for these to roll in.

IMPACT FACTOR

Finally to the issue of impact factor, with which our funding authorities appear so infatuated. After disappearing into the ether as a result of our name change we have re-emerged with an unprecedented factor of 2.1 (fig 1). For those who may not be too familiar with it let me clarify the mathematical conjuring tricks which resulted in that figure. Impact factors are derived by dividing all the citations of the previous 2 years by the number of articles published in a given journal. There are a few exceptions. For example, letters count as citations but not as articles. When conference abstracts are cited, an increasing and questionable practice, they are considered bona fide citations though the original abstract is not counted as a publication. The same is true for supplements.

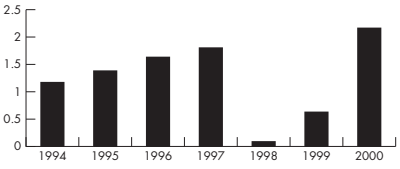

Figure 1 Impact factor of STI.

You can see where this illogical juggling leads: journals with a large correspondence, or which publish conference abstract and supplements do well. More questionably, clinical journals do worse than pure science journals. This is because clinical research takes longer to perform than laboratory based research. Hence the "impact" of clinical studies is longer—and certainly way beyond the arbitrary 2 year cutoff point. The final point to make is that the impact factor usually reflects the "impact" of one or two articles with high citations and is therefore more realistically the impact factor of an article rather than the journal as a whole. As you see, this is an imperfect measure of the quality of a journal. But it is all we have. The Americans, rightly I think, ignore it. The rest of the world are unnaturally wedded to it.

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